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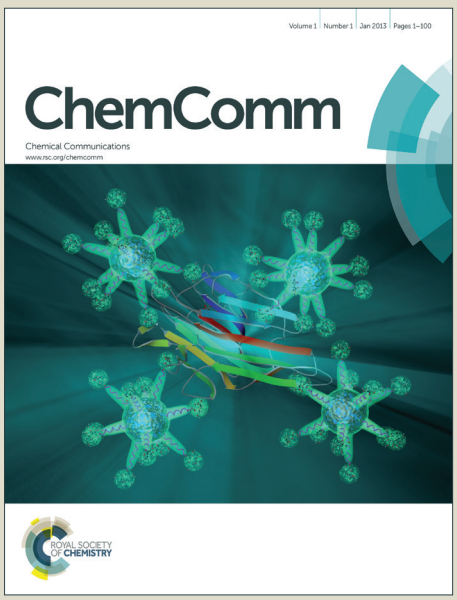

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Construction of dibenzo-fused seven- to nine-membered carbocycles via Brønsted acid-promoted intramolecular Friedel–Crafts-type alkenylation

Takashi Otani,*[a] Kanako Ueki,[b] Kinryo Cho,[b] Kan Kanai,[b] Kotaro Tateno[b] and Takao Saito*[ab]

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Brønsted acid-promoted intramolecular hydroarylation of alkynylbenzenes carrying an arylalkyl group at the ortho-position leads to alkylidenedibenzo[*a*,*d*]cycloheptenes, -octenes and -nonenes in up to quantitative yield with complete regioselectivity. The scope and limitation of this reaction and application to the synthesis of tricyclic antidepressants are described.

5-Alkylidene-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptenes **1** are an important structural motif found in many biologically active compounds, as exemplified by tricyclic antidepressants (TCAs). For example, amitriptyline (**1a**),[1,2] which has been prescribed since the 1950s, has been the most widely used TCA to treat a number of mental disorders. Structurally similar nortriptyline (**1b**)[3] is also one of the often-prescribed TCAs.

Because of their medical importance, various synthetic methods for **1** have been developed to date.[2,4] Widely reported syntheses of **1** exploit the corresponding ketone (dibenzosuberone (**4**)) backbone; treatment of dibenzosuberone with Grignard reagent (R^1CH_2MgX) and the following elimination of water from the resulting carbinol complete the synthesis of **1** (Fig. 1, eqn (1)).[2] This protocol is quite practical to access the seven-membered ring system **1**, but is unattractive to construct the homologous eight-[5] and nine-membered[6] ring systems **2** and **3** because the corresponding ketone precursors **5** and **6** are not commercially available nor easily prepared. Indeed, access to the nine-membered ring system is very difficult, and to our knowledge, synthesis of 13-alkylidene-6,7,8,13-tetrahydro-5*H*-dibenzo[*a*,*d*]cyclononene **3** has not been achieved to date.[7]

Palladium-catalysed alkenylation (i.e., reductive Heck reaction)[8,9] and gold, platinum or gallium-catalysed Friedel–Crafts (F.C.)-type alkenylation[10] of alkynylbenzenes carrying a heteroatom-tethered aryl group in the ortho-position have emerged as useful reactions for the synthesis of benzo- or dibenzo-fused seven- and eight-membered oxygen- and nitrogen-heterocycles. Curiously, however, these types of reactions have not been applied for the synthesis of the all-carbon counterparts **1–3**.[11,12] Concerning F.C.-type alkenylations, other groups[13] and we[14] have demonstrated that strong Brønsted acids,[15] such as trifluoromethanesulfonic (triflic) acid (TfOH), are more highly active promoters than Lewis acids in several reactions.[16] This background prompted us to investigate intramolecular F.C.-type hydroarylation of o-alkyn-1-yl(arylalkyl)benzenes **7–9** leading to dibenzo-fused seven- to nine-membered carbocycles **1–3** (eqn (2)).

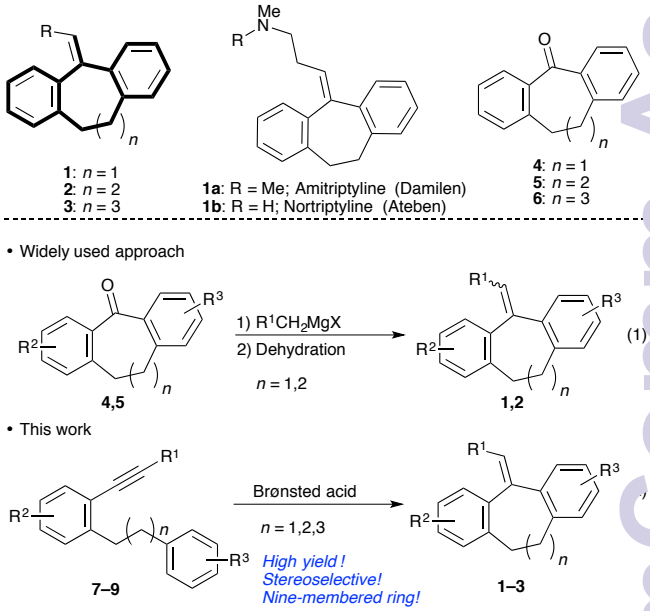
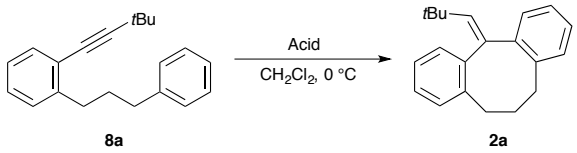


Fig. 1.

We initially examined the feasibility of a Brønsted acid catalysed cyclization of 1-(3,3-dimethyl-1-butyn-1-yl)-2-(3-phenylpropyl)benzene (**8a**) to dibenzocyclooctene derivative **2a** in dichloromethane at 0 °C (Table 1). When **8a** was treated with 10 mol% of triflic acid for 4 h, the reaction did not complete and formed **2a**, albeit in a low yield of 21% (entry 1). The yield of **2a** was improved by increasing the amount of triflic acid (entries 2 and 3), and the use of 100 mol% resulted in quantitative formation of **2a** in the short reaction time of 10 min (entry 4). Other strong acids such as bis(trifluoromethane)sulfonimide (entry 5) and sulfuric acid (entry 6) also facilitated this reaction; however, trifluoroacetic acid and hydrogen chloride (ether solution) showed almost no activity (entries 7 and 8). We also examined a cationic gold(I) complex (5 mol%) prepared from AuCl(PPh_3) with AgOTf; however, the reaction formed only a trace amount of **2a** in spite of stirring at room temperature for 1 h followed by heating at reflux for 1 h in chloroform (entry 9).[17]

Table 1 Optimization of acids



8a **2a**

Entry	Acid	mol%	Time (min)	**2a** (%)	**8a** (%)
1	TfOH	10	240	21	62
2	TfOH	20	60	44	44
3	TfOH	50	20	90	—
4	TfOH	100	10	99	—
5	Tf_2NH	100	10	79	—
6	H_2SO_4	100	45	91	—
7	HCl[a]	100	60	ND[b]	90
8	CF_3CO_2H	100	1440	4	74
9[c]	Au(OTf)PPh_3[d]	5	120[e]	ND[b]	92

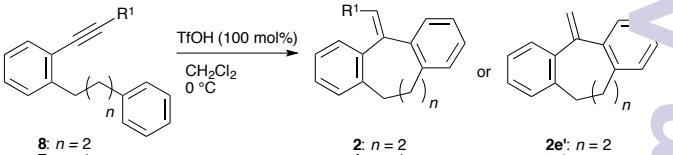
[a] Hydrogen chloride ether solution (1.0 M) was used. [b] Not detected. [c] In chloroform. [d] Prepared from AuCl(PPh_3) with AgOTf. [e] 60 min at room temperature and 60 min at 50 °C.

With the effective reaction conditions in hand, we explored the compatibility of substituents on the alkyne terminus for the synthesis of dibenzocyclooctene and -heptene derivatives (Table 2). Secondary and primary alkyl groups, such as isopropyl and propyl groups, are more suitable groups for this reaction (entries 1 and 2). However, phenyl-substituted **8d** produced a complex mixture without formation of the cyclized product **2d** (entry 3), and the TMS-substituted **8e** produced TMS-group eliminated exo-methylene compound **2e′** in 9% yield (entry 4). The conditions are applicable for construction of a seven-membered ring system **1** (n = 1), and **1c**, **1d** and **1e′** were synthesized from **7c–e** in good to high yields (entries 5–7).

To demonstrate the utility of this protocol for the synthesis of medicines, amitriptyline (**1a**), nortriptyline (**1b**) and their derivatives were targeted. Although these reactions required 5 equiv of triflic acid, the cyclization of **7a** and **7b** produced **1a** and **1b** in 56% and 68% yields, respectively (entries 8 and 9). Similarly, substrates **7f** and **8f–h** having hydroxyl or primary amino groups were also tolerant under the super acidic conditions and the corresponding alcohols and amines were obtained in acceptable yields (entries 10–13).

Next, we examined the effects of the substituents on the aromatic rings and stereoselectivity of the addition process (Table 3). The reaction of **8i**, in which a methoxy group was installed in the phenylene moiety (R^2), with triflic acid, afforded the corresponding adduct **2i** as a mixture of *syn*- and *anti*-addition products, along with dimer **10** (entry 1). In contrast, less acidic sulfuric acid produced *syn*-addition product (*Z*)-**2i** exclusively in moderate yield (entry 2). Similarly, the reaction of **8j**, having a methoxy group at R^3 on the pendant aryl group, with triflic acid produced a mixture of *syn*- and *anti*-adducts **2i**, whereas sulfuric acid delivered *syn*-addition product (*E*)-**2i** with complete selectivity (entry 3 vs. 4). The separate formation of (*E*)-**2i** and (*Z*)-**2i** from **8i** and **8j**, respectively (entries 2 and 4), indicates that both *syn*-addition products are kinetic products. To prove further the above-mentioned product selectivity, we also examined the triflic and sulfuric acid promoted reaction of methyl-substituted substrates **8k**, **8l** and **7g** (entries 5–9). Consistent with the above, sulfuric acid delivered *syn*-addition products highly selectively (entries 6, 7 and 9), while triflic acid produced almost 1:1 mixtures of *syn*- and *anti*-addition products with high combined yields (entries 5 and 8). The structures of (*Z*)-**2j** and (*E*)-**1g** were unambiguously confirmed by X-ray crystal analysis. The reaction of **7h** bearing the electron-withdrawing trifluoromethyl group on the pendant aryl group (R^3), with triflic acid formed a mixture of *syn*- and *anti*-adducts ((*E*)- and (*Z*)-**1h**) along with a small amount of *t*-butyl-eliminated compound **1h′** (entry 10); however, the reaction with sulfuric acid was completely suppressed (entry 11). The reaction of **7i**, bearing an *n*-propyl group on the

Table 2 Synthesis of dibenzocycloheptenes and -octenes having various substituents on the alkyne terminus

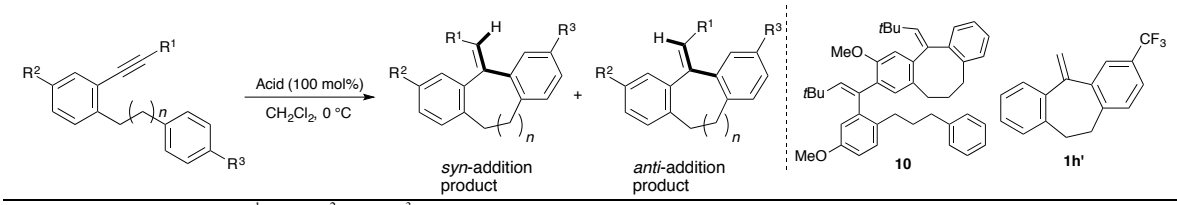


8: n = 2 **7**: n = 1 **2**: n = 2 **1**: n = 1 **2e'**: n = 2 **1e'**: n = 1

Entry	S.M.	n	R^1	Time (min)	Product (yield)
1	**8b**	2	*i*Pr	10	**2b** (85)
2	**8c**	2	*n*Pr	10	**2c** (75)
3	**8d**	2	Ph	40	**2d** (ND)[a]
4	**8e**	2	TMS	30	**2e′** (9)
5	**7c**	1	*t*Bu	10	**1c** (97)
6	**7d**	1	*n*Pr	15	**1d** (96)
7	**7e**	1	TMS	20	**1e′** (50)
8[b]	**7a**	1	$CH_2CH_2NMe_2$	10	**1a** (56)
9[b]	**7b**	1	CH_2CH_2NHMe	10	**1b** (68)
10[b]	**7f**	1	CH_2CH_2OH	10	**1f** (44)
11[b]	**8f**	2	$CH_2CH_2NMe_2$	10	**2f** (48)
12[b]	**8g**	2	CH_2CH_2OH	10	**2g** (34)
13[b]	**8h**	2	$CH_2CH_2NH_2$	10	**2h** (25)

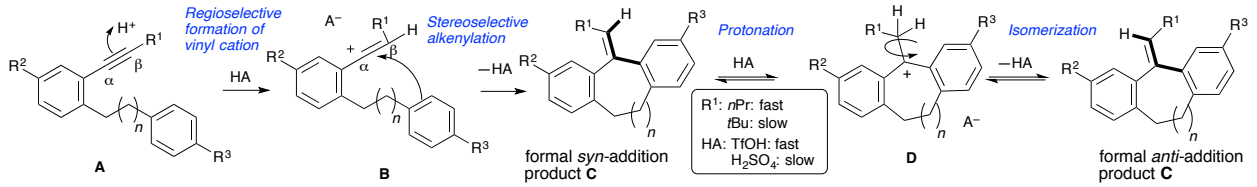
[a] Not detected. [b] 5 equiv of TfOH were used.

Table 3 Effects of substituents on aromatic groups



Entry	S.M.	*n*	R^1	R^2	R^3	Acid	Time (min)	*syn*-addition product	*anti*-addition product	Yield[a]	Ratio (*syn*-:*anti*-addition product)[b]
1	**8i**	2	*t*Bu	OMe	H	TfOH	10	*Z*-**2i**	*E*-**2i**	72[d]	79:21
2	**8i**	2	*t*Bu	OMe	H	H_2SO_4	10	*Z*-**2i**	*E*-**2i**	54[e]	>99:1
3	**8j**	2	*t*Bu	H	OMe	TfOH	30	*E*-**2i**	*Z*-**2i**	92	79:21
4	**8j**	2	*t*Bu	H	OMe	H_2SO_4	10	*E*-**2i**	*Z*-**2i**	45	>99:1
5	**8k**	2	*t*Bu	Me	H	TfOH	10	*Z*-**2j**	*E*-**2j**	quant.	45:55
6	**8k**	2	*t*Bu	Me	H	H_2SO_4	20	*Z*-**2j**	*E*-**2j**	quant.	>99:1
7	**8l**	2	*t*Bu	H	Me	H_2SO_4	20	*E*-**2j**	*Z*-**2j**	86	>99:1
8	**7g**	1	*t*Bu	H	Me	TfOH	10	*E*-**1g**	*Z*-**1g**	94	50:50
9	**7g**	1	*t*Bu	H	Me	H_2SO_4	10	*E*-**1g**	*Z*-**1g**	95	99:1
10	**7h**	1	*t*Bu	H	CF_3	TfOH	10	*E*-**1h**	*Z*-**1h**	35[f]	55:45
11	**7h**	1	*t*Bu	H	CF_3	H_2SO_4	60	*E*-**1h**	*Z*-**1h**	N.R.	
12	**7i**	1	*n*Pr	H	Me	TfOH	10	*E*-**1i**	*Z*-**1i**	91	50:50
13	**7i**	1	*n*Pr	H	Me	H_2SO_4[g]	25[h]	*E*-**1i**	*Z*-**1i**	66	60:40
14	**7i**	1	*n*Pr	H	Me	H_2SO_4	20	*E*-**1i**	*Z*-**1i**	9	>95:5

[a] Combined yield of *syn*- and *anti*-addition product. [b] Determined by ^{1}H NMR. ">99:1" denotes no *anti*-addition product was observed by ^{1}H-NMR. [d] Dimer **10** was obtained in 13% yield. [e] Dimer **10** was obtained in 1% yield. [f] **1h'** was also obtained in 10% yield. [g] Additional 1 equiv of H_2SO_4 was added after 15 min. [h] Total time.



Scheme 1 Possible reaction pathway

alkyne terminus (R^1), with triflic acid also proceeded efficiently (entry 12). However, the reaction of **7i** with sulfuric acid is slower than that of the *t*-butyl counterpart **7g**, and thus a longer reaction time and addition of another equivalent of sulfuric acid were required for full conversion of **7i**, which resulted in the formation of *syn*- and *anti*-addition products **1i** (60:40, entry 13). Finally, we found that quenching the reaction before complete consumption of **7i** forms stereochemically pure *syn*-addition product (*E*)-**1i**, albeit in 9% yield (entry 14).

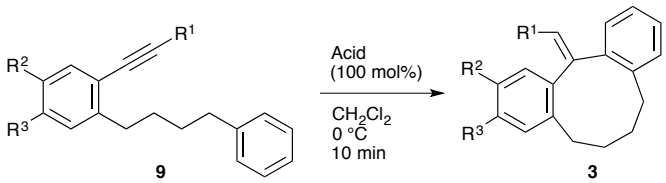
Based on the above results, we propose a possible reaction pathway (Scheme 1). By treatment with a Brønsted acid, regioselective protonation of the β-carbon atom of **A** forms a relatively stable benzylic vinyl cation **B**, after which the pendant aryl group attacked the α-carbon atom from the less hindered H-side in a F.C. manner to give the formal *syn*-addition product **C**. Under the super acidic conditions, however, olefin isomerization of the *syn*-addition product **C** occurs, which results in the formation of a mixture of *syn*- and *anti*-addition products **C**. Table 3 suggests that triflic acid rather than sulfuric acid and the smaller *n*-propyl group rather than the *t*-butyl group promote the rapid olefin isomerization.

To evaluate further the scope of this protocol, the construction of a nine-membered ring was explored (Table 4). Gratifyingly, triflic acid promoted the cyclization of **9** to **3**, albeit in moderate yields (entries 1, 3–8), but the reaction of **9a** with sulfuric acid formed only a complex mixture (entry 2). It is noteworthy that the flexible butylene chain-tethered aryl group participated in a formal 9-*exo*-dig cyclization.[12] In addition, oxidative cleavage of the alkene double bond[18] of **3b** led to the corresponding ketone **6** in 61% yield (eqn (3)). Ketone **6** would serve as a practical building block for the synthesis of dibenzocyclononene derivatives.

In summary, we have developed a Brønsted acid-promoted intramolecular Friedel–Crafts-type alkenylation that produces dibenzo-fused seven- to nine-membered carbocycles in up to quantitative yield with up to complete control of the olefin

geometry, and achieved construction of dibenzo-fused cyclononene derivatives **3** for the first time.

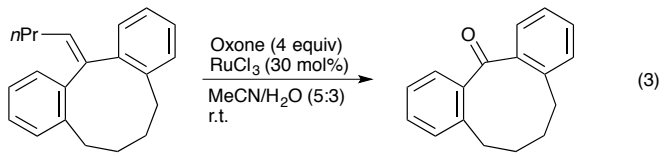
Table 4 Synthesis of dibenzocyclononenes



9 **3**

Entry	S.M.	R^1	R^2	R^3	Acid	Product (%)
1	**9a**	*t*Bu	H	H	TfOH	**3a** (43)
2	**9a**	*t*Bu	H	H	H_2SO_4	**3a** (ND)[a]
3	**9b**	*n*Pr	H	H	TfOH	**3b** (42)
4	**9c**	*n*Pent	H	H	TfOH	**3c** (39)
5	**9d**	*t*Bu	Me	H	TfOH	**3d** (43)[b]
6	**9e**	*n*Pr	Me	H	TfOH	**3e** (40)[c]
7	**9f**	*t*Bu	H	Me	TfOH	**3f** (42)[d]
8	**9g**	*n*Pr	H	Me	TfOH	**3g** (31)[d]

[a] Not detected. [b] Major:minor = 52:48. [c] Major:minor = 74:26. [d] Major:minor = 51:49.



3b **6** (61%) (3)

Notes and references

[a] Research Center for Chirality, Research Institute for Science & Technology, Tokyo University of Science, Kagurazaka, Shinjuku, Tokyo 162-8601, Japan.
[b] Department of Chemistry, Faculty of Science, Tokyo University of Science, Kagurazaka, Shinjuku, Tokyo 162-8601, Japan.
E-mail: totani@rs.tus.ac.jp (T.O.); Fax: +81 (0)3-5261-4631
E-mail: tsaito@rs.kagu.tus.ac.jp (T.S.); Fax: +81 (0)3-5261-4631

† Electronic supplementary information (ESI) available: Experimental details, characterization data and NMR spectra. CCDC 1047277 ((*Z*)-**2j**) and 1047278 ((*E*)-**1g**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b000000x//

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